Risk Assessment of Low-level Chemical Exposures from Consumer Products under the U.S. Consumer Product Safety Commission Chronic Hazard Guidelines

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The U.S. Consumer Product Safety Commission (CPSC) is an independant regulatory agency that was created in 1973. The CPSC has jurisdiction over more the 15,000 types of consumer products used in and around the home or by children, except items such as food, drugs, cosmetics, medical devices, pesticides, certain radioactive materials, products that emit radiation (e.g., microwave ovens), and automobiles. The CPSC has investigated many low-level exposures from consumer products, including formaldehyde emissions from urea-formaldehyde foam insulation and pressed wood products, CO and NO_2 emmisions from combustion appliances, and dioxin in paper products. Many chemical hazards are addressed under the Federal Hazardous Substances Act (FHSA), which applies to acute and chronic health effects resulting from high- or low-level exposures. In 1992 the Commission issued guidelines for assessing chronic hazards under the FHSA, including carcinogenicity, neurotoxicity, reproductive/developmental toxicity, exposure, bioavailability, risk assessment, and acceptable risk. The chronic hazard guidelines describe a series of default assumptions, which are used in the absence of evidence to the contrary. However, the guidelines are intended to be sufficiently flexible to incorporate the latest scientific information. The use of alternative procedures is permissible, on a case-by-case basis, provided that the procedures used are scientifically defensible and supported by appropriate data. The application of the chronic hazard guidelines in assessing the risks from low-level exposures is discussed. — *Environ Health Perspect* 106(Suppl 1):387–390 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-1/387-390babich/abstract.html*

Key words: risk assessment, chronic hazard, consumer product, carcinogen, hazardous substance

Introduction

The U.S. Consumer Product Safety Commission (CPSC) is an independent regulatory agency that was created in 1973. The CPSC has jurisdiction over more than 15,000 types of consumer products used in and around the home or by children, except items such as food, drugs, cosmetics, medical devices, pesticides, certain radioactive materials, products that emit radiation (e.g., microwave ovens), and automobiles (*1*). Some low-level exposures that the CPSC has investigated include: asbestos in plaster products (*2*); formaldehyde emissions from urea-formaldehyde foam insulation (*3*) and pressed wood products (*4*); tris(2,3-dibromopropyl) phosphate flame retardant in children's sleepwear (*5*); nitrosamines in infant pacifiers (*6,7*); CO and NO_2 emissions from combustion appliances (*8,9*); polycyclic aromatic hydrocarbon emissions from wood stoves (*10*); methylene chloride in paint removers and other products (*11–14*); volatile organic compound emissions from carpets (*15*) and carpet cushions (*16*); and dioxin in paper products (*17*).

The statutes administered by the CPSC that address chemical or toxic hazards include the Consumer Product Safety Act, Federal Hazardous Substances Act (FHSA), and Poison Prevention Packaging Act. The CPSC has a range of risk-management options available, including information and education, voluntary standards, mandatory labeling, mandatory performance standards, recalls, and bans. Many chemical hazards are addressed under the FHSA, which applies to acute and chronic health effects resulting from high- or low-level exposures. Under the FHSA the least burdensome option that adequately addresses the hazard at issue must be applied and the expected benefits of that action must bear a reasonable relationship to the costs (*18*).

Discussion

Under the FHSA (*19*), the term hazardous substance is defined as:

> Any substance or mixture of substances which (i) is toxic, (ii) is corrosive, (iii) is an irritant, (iv) is a strong sensitizer, (v) is flammable or combustible, or (vi) generates pressure though decomposition, heat, or other means, if such a substance may cause substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use [emphasis added], including reasonably foreseeable ingestion by children.

This definition has several implications for how the CPSC staff performs risk assessments and which products are regulated. Regulatory decisions are risk based. Thus, exposure and bioavailability must be considered in addition to toxicity (*20*). This is in contrast to some of the hazard assessment procedures used by other federal agencies. For example, under the Occupational Safety and Health Administration's hazard communication standard (*21*), a component of a mixture that is present at < 1%, or 0.1% for a carcinogen, may be exempt from labeling and does not need to be considered in the hazard determination. On the other hand,

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Abbreviations used: ADI, acceptable daily intake; CPSC, U.S. Consumer Product Safety Commission; FHSA, Federal Hazardous Substances Act; MLE, maximum likelihood estimate; PBPK, physiologically based pharmacokinetic; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; U.S. EPA, U.S. Environmental Protection Agency; U.S. FDA, Food and Drug Administration.

the presence of a toxic ingredient would not automatically trigger a regulation. Under the hazard communication standard, any carcinogen present at > 0.1% is considered hazardous regardless of the risk (*21*). The properties of mixtures, rather than individual ingredients, are generally considered under the FHSA (*19*).

The FHSA does not provide for premarket registration or premarket approval. This places the burden on manufacturers to ensure that products either are not hazardous or that they are properly labeled. Also, the FHSA does not include specific criteria for assessing chronic hazards. In 1992, the Commission issued guidelines for assessing chronic hazards under the FHSA, including carcinogenicity, neurotoxicity, reproductive/developmental toxicity, exposure, bioavailability, risk assessment, and acceptable risk (*20*). The methods that the CPSC staff uses to assess chronic hazards are generally similar to those of other federal agencies, with certain exceptions. The chronic hazard guidelines describe a series of default assumptions that are used in the absence of evidence to the contrary. However, the guidelines are intended to be sufficiently flexible to incorporate the latest scientific information. Deviation from the default procedures is permissible provided that the procedures used are scientifically defensible and supported by appropriate data.

Based on the chronic hazard guidelines, studies in humans and animals are classified as providing inadequate, limited, or sufficient evidence of toxicity. A substance or mixture is considered toxic under the FHSA if there is at least limited evidence of toxicity in humans or sufficient evidence in animals. For carcinogens the multistage model is the default procedure for high-to-low dose extrapolation (Table 1). The CPSC differs from the U.S. Environmental Protection Agency (U.S. EPA) (*22*) and the U.S. Food and Drug Administration (U.S. FDA) (*23–25*) in that the maximum likelihood estimate (MLE) of risk is used, provided that the parameter q_1 is nonzero, that is, that the MLE is linear at low doses (*20*). The surface area correction is used for animal-to-human extrapolation; surface area correction is used by the U.S. EPA (*22*) but not by the U.S. FDA (*25*). Pharmacokinetic modeling may be used to extrapolate from route to route, high to low dose, or one exposure regimen to another, but not for animal-to-human extrapolation (*20*). In contrast to the U.S. EPA (*22*), an increased incidence of benign tumors may contribute to a finding of sufficient evidence of carcinogenicity in animals if the benign tumors have the potential to progress to malignancy (*20*). Tumors at independent sites in the same laboratory animal are considered separate responses and therefore could support a finding of sufficient evidence of carcinogenicity in animals (*20*). These differences are subject to change, however, as new risk-assessment methods are adopted (*24,26*).

The default procedure for assessing noncancer end points is essentially a safety factor approach (*20*). For both cancer and noncancer end points, an acceptable daily intake (ADI) is calculated. A substance is considered hazardous under the FHSA if the ADI is exceeded during "reasonably foreseeable handling and use" (*19*).

Reasons for the differences in risk assessment procedures among federal agencies are discussed in detail elsewhere (*20,23,27*). Some of these differences reflect differences in the agencies' missions and the statutes that they administer; others are in areas of scientific uncertainty (*20,23,27*). Although they use different procedures, the cancer potency estimates derived by the CPSC, the U.S. EPA, and the U.S. FDA generally fall within a 10-fold range (*25*). The difference in potency estimates is mainly attributable to the method of animal-to-human extrapolation (surface area or body weight) and choice of risk metric (MLE or upper bound) (Table 1). The CPSC works closely with other federal agencies on issues that cross jurisdictional boundaries, such as methylene chloride (*28*), dioxin in paper products (*25*), and indoor air quality (*29*), and has participated in efforts to harmonize risk-assessment procedures among federal agencies (*30*).

Table 1. Comparison of quantitative cancer risk assessment procedures used by federal regulatory agencies.

Agency	Dose–response model	Dose–response metric	Animal-to-human extrapolation
CPSC	Multistage	Maximum likelihood	Surface area
U.S. EPA	Multistage	Upper bound	Surface area
U.S. FDA	Gaylor–Kodell	Upper bound	Body weight
OSHA	Multistage	Maximum likelihood	Body weight

Sources: CPSC (*20*), U.S. EPA (*22,25*), Lorentzen (*23*), Gaylor (*24*), and Rhomberg (*27*).

Three questions posed regarding how regulatory/public health agencies consider the biological effects of low-level exposes are as follows:

First, does the understanding of the mechanisms of toxicity affect how the CPSC assesses risks from exposures to toxic substances? Knowledge of the mechanism or mode of action is incorporated into the risk-assessment process. The CPSC chronic hazard guidelines describe a series of default assumptions to be used in the absence of information to the contrary. The principal issue regarding mechanistic information is not whether it should be incorporated into the risk-assessment process, but whether there is sufficient information in a particular case to deviate from the default assumptions (*20*). For example, a knowledge of the mechanism of action of certain chemicals that cause tumors in the male rat kidney suggests that this mechanism is not relevant in humans (*31*). This conclusion has been supported by a considerable body of evidence and there is general agreement in the scientific community. Therefore, chemicals acting by this mechanism would be considered toxic under the FHSA, as they would under the default assumptions.

Second, does an understanding of the mechanisms by which the body adapts (e.g., detoxifies, repairs, etc.) to the effects of exposures to toxic substances affect how the CPSC assesses risks from exposures to toxic substances? An understanding of the mechanisms by which the body detoxifies or repairs the effects of toxic substances can be incorporated into the risk-assessment process. Pharmacokinetic information describes the manner in which some chemicals are detoxified as well as activated. Physiologically based pharmacokinetic (PBPK) models may be used to incorporate pharmacokinetic information into the risk-assessment process. One critical issue in developing PBPK models is the choice of dose surrogate. The dose surrogate might be the concentration of a toxicologically relevant metabolite in the target tissue. The dose surrogate should be directly and quantitatively related to the toxic end point of interest. For example, CPSC staff incorporated a PBPK model into its methylene chloride cancer risk assessment (*12–14*). Methylene chloride is metabolized by two pathways: a glutathione *S*-transferase pathway that is believed to activate methylene chloride and a mixed-function oxidase pathway that may be considered to detoxify. In this case, the dose surrogate was the amount of methylene chloride metabolized by the glutathione *S*-transferase pathway in the the

target tissue. Because the risk in humans was estimated from animal studies, PBPK models were developed and validated for humans as well as for animals (*12–14*).

DNA repair is another type of recovery process that repairs damage induced by carcinogens. Thus, some authors have proposed the use of DNA adducts as measures of internal dose in risk assessment (*32–37*). As with PBPK models, the choice of dose surrogate is a critical issue. The particular adduct used as the the dose surrogate should be the cause of the tumors, the tumor response should be directly related to the adduct level, and the relationship between adduct level and tumor response should be constant with dose (*36,37*). Many chemical carcinogens induce multiple DNA adducts. For example, alkylating agents induce a spectrum of adducts, including O^6-alkylguanine and O^4-alkylthymine (*38–41*). O^6-alkylguanine is considered procarcinogenic in the induction of nervous system (*42*) and mammary (*43*) tumors in animals. However, in rats continuously exposed to diethylnitrosamine, O^4-ethylthymine accumulated in hepatocyte DNA, whereas O^6-ethylguanine levels declined to nondetectable levels because of the more efficient repair of O^6-ethylguanine (*34,35*). Therefore, O^4-ethylthymine may be more important than O^6-ethylguanine in the induction of hepatocellular tumors in rats (*34,35*).

Once the procarcinogenic adduct is identified, other issues remain: *a*) DNA adducts may not be uniformly distributed throughout the genome (*44*); *b*) DNA repair may be targeted to actively transcribed genes (*45*) and to the transcribed strand (*46*); *c*) mutational hot spots appear to play an important role in carcinogenesis in humans (*47–49*); *d*) cell replication, the rate of which may vary among different organs and cell types (*33,35*), is required for mutagenesis to occur. Therefore, there might not be a direct relationship between adduct levels in bulk DNA and tumor response (*33–37*).

Third, if low doses of toxic agents induce apparently beneficial responses (e.g., enhanced longevity, lower incidence of disease), how does and/or could the CPSC address this? The FHSA only defines toxic and hazardous. It does not define nontoxic or nonhazardous and it does not address beneficial effects. Therefore, beneficial effects per se could not be addressed under the FHSA: only the potential hazards could be addressed. Any product that claimed a beneficial effect could be under the jurisdiction of other federal agencies.

There are at least two situations in which a low dose of a toxic agent could induce apparently beneficial effects. In one situation the agent has no effect or a beneficial effect at low levels and is toxic at higher levels; that is, a threshold or a J-shaped dose–response curve, respectively. Whereas regulatory decisions under the FHSA are risk based, the key issue is whether the exposures that would occur during "reasonably foreseeable handling and use" (*19*) would present a hazard.

In the second situation a low-level exposure at subtoxic doses could induce a defense mechanism that protects against a subsequent potentially toxic exposure; the risk would depend on a prior exposure at the lower dose. The pertinent issue is whether the prior low-level exposure is likely to occur during "reasonably foreseeable handling and use" (*19*). One might also consider whether the ability to induce the appropriate defense mechanism is universal or whether some individuals might be deficient in the inducible defense mechanism and thus be more susceptible.

Conclusions

The CPSC chronic hazard guidelines were issued in 1992 (*20*). They were not intended to be applied mechanically. Rather, the guidelines are sufficiently flexible to allow professional judgment and the latest science to be incorporated into the risk-assessment process. The default assumptions are meant to be used only in the absence of evidence to the contrary. Alternative methods may be substituted for the default assumptions on a case-by-case basis, provided that they are supported by appropriate data and are scientifically defensible. However, CPSC staff considers that some changes from the default procedures could have a profound effect on the outcome of a risk assessment. For example, substituting a threshold-distribution model for the multistage model in cancer risk assessment could reduce the risk estimate by orders of magnitude. Such a change should be made only when there is a considerable body of evidence to support it and a degree of scientific consensus exists. The nongenotoxic carcinogen 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) appears to act through a receptor-mediated mechanism (*50,51*). An early step in TCDD-induced carcinogenesis is believed to be binding to the aryl hydrocarbon receptor, which leads to alterations in the expression of certain genes. Extensive study of the effects of TCDD on gene expression suggests that receptor-mediated mechanisms may result in either linear or nonlinear responses at low doses (*52,53*). Therefore, the knowledge that a certain carcinogen is nongenotoxic or acts through a receptor is in itself insufficient to abandon the default procedure for high-to-low dose extrapolation.

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